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Treatment of Pediatric Malignant Thymoma: Long-Term Remission in a 14-Year-Old Boy With EBV-Associated Thymic Carcinoma by Aggressive, Combined Modality Treatment

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Malignant thymoma, including thymic carcinoma, is extremely uncommon in the pediatric population. It is known to have a very poor outcome. We report on a 14-year-old boy with Epstein-Barr virus (EBV)-associated thymic carcinoma. Sections of the original tumor were analyzed for EBV by in situ hybridization to confirm the histological diagnosis of a lymphoepithelioma-like subtype. High copy numbers of EBV RNA were detected in the tumor tissue, suggesting an etiological role of EBV in our case. Intensive treatment resulted in long-term remission over 12 years. In order to facilitate the difficult management of the rare child with malignant thymoma, a literature search was initiated. Forty well-documented pediatric cases of malignant thymoma were found in the literature. Histological characteristics, clinical features, and therapeutic regimens were reviewed. Having the very limited experience with malignant thymoma in childhood in mind, it is concluded that its aggressiveness makes the most intensive treatment necessary. Long-term remission can be achieved by application of radical surgery, high-dose irradiation, and multiagent chemotherapy. The combination of cisplatinum, etoposide, and ifosfamide seems to be promising.

Key words: thymic carcinoma, children, Epstein-Barr virus, chemotherapy, surgery, radiation therapy

INTRODUCTION

The thymus is composed of epithelial and non-epithelial cells, such as thymocytes and other mesenchymal cells. Histopathologically malignant thymomas in children and adults are defined as tumors, that derive exclusively from epithelial cells [1,2]. Malignant thymomas are cytologically further classified in category I, with no or minimal cytologic atypia, and category II, representing cytologically malignant variants (Table I). Category II malignant thymomas are also regarded as thymic carcinomas. Prompted by the successful treatment of a patient with an EBV-associated thymic carcinoma at the Department of Pediatric Oncology and Hematology of the Heinrich Heine Universität Düsseldorf, a literature search (MEDLINE, 1982–1994) was carried out. Fourty well-described cases of malignant thymoma and thymic carcinoma in children were identified [4–13]. Thymic cysts and lymphomas, as well as germ cell tumors of the thymus, which were included in reviews about thymomas in children [6,7], were regarded as different disease entities and were not included in this review. We report on a 14-year-old boy with EBV-associated thymic carcinoma who is in long-term remission, achieved by intensive combined-modality treatment.

CASE REPORT

A 14-year-old boy of Portuguese origin noted that he was pale and complained of losing weight over 1 month, although he had a normal appetite. On physical examination the boy was in a poor nutritional condition and had marked clubbing. Inspection was remarkable for a somewhat bulged-out right anterior chest wall. Neurological examination was normal. Laboratory investigations on admission showed an elevated Westergren erythrocyte sedimentation rate of 94 mm/h and hypergammaglobulinemia. Epstein-Barr virus (EBV) serology was not available. The chest x-ray showed an anterior mediastinal mass. It extended from the sternoclavicular region down

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TABLE I. Classification of Malignant Thymomas According to Levine and Rosai [3]

I.	With no or minimal cytological atypia
	a. Locally invasive (usual form)
	b. With true lymphatic or hematogenous spread (rare)
II.	Cytologically malignant morphological variants (=thymic carcinoma)
	a. Squamous cell carcinoma
	b. Lymphoepithelioma-like carcinoma
	c. Clear cell carcinoma
	d. Sarcomatoid carcinoma
	e. Undifferentiated carcinoma

to the diaphragm as documented by computed tomography (CT). Bone marrow puncture did not show malignant cells. Bone metastases were excluded by a negative bone scan and a bone biopsy of the left olecranon. The latter was initiated because of periosteal new bone formation in that area seen on a conventional x-ray.

Surgical exploration 12 days after admission revealed a large and infiltrating tumor. Resection of the tumor included the upper and middle lobe of the right lung, parts of the pericardium, and the anterior part of the superior vena cava and the vena azygos.

Histopathological examination of the tumor tissue (Fig. 1) showed epithelial tumor cells forming solid cords and infiltrating soft tissue, as well as neighboring lymph nodes. Nuclei were round in shape and large in size, with prominent, central nucleoli and a relatively bright chromatin. The borders of the cytoplasm could not clearly be demarcated. Between tumor cell aggregates, clusters of lymphocytes and some plasma cells were found. The tumor was therefore classified as lymphoepithelioma-like carcinoma of the thymus, indistinguishable from undifferentiated carcinoma of nasopharyngeal type in 1981.

At that time no molecular biology techniques were available to examine EBV in the tissue. EBV RNA was demonstrated in paraffin-embedded tissue sections of the original tumor more than a decade later. The method is described by Brousset et al. [14] and is used routinely for EBV detection in the laboratory of Pediatric Pathology at the University of Kiel. In situ hybridization with an EBV-specific, biotinylated DNA probe was followed by immunohistochemistry that clearly showed nuclear expression of viral transcripts (Fig. 2).

One month after the operation, a pericardial effusion was noted in our patient, and further examination by CT indicated a local relapse of the tumor surrounding the pulmonary arteries and the aorta, resulting in left ventricular failure. The patient now received a combination chemotherapy with eight courses of intravenous vinblastin (4.0 mg/m^2) on the first day, cisplatin (25 mg/m^2) over 5 hours for 5 days, Adriamycin (20 mg/m^2) for 3 days over 24 hours, bleomycin (10 mg/m^2) for 3 days over 24 hours, and oral prednisone (60 mg/m^2) for 5 days over 5 months. Chemotherapy was followed by local irradiation with 40 Gy.

Fourteen months after initial presentation, a second relapse occurred in a left supraclavicular lymph node, which was confirmed by biopsy. This time the patient received four cycles of chemotherapy over four months, consisting of etoposide (100 mg/m^2) for 3 days, and cisplatin (20 mg/m^2) and ifosfamide (2 g/m^2) from day 1 to 5. Again, chemotherapy was followed by local irradiation with 40 Gy.

EBV serology was first obtained 2 years after admission and showed a positive VCA-IgG (1:1,280) and a negative VCA-IgM titer. VCA-IgA was not available. Prior to this finding the patient had received three blood transfusions for chemotherapy-induced aplasia.

As late sequelae of the combined-modality treatment, the patient has a marked scoliosis, causing a restricted pulmonary function with a reduced vital capacity and a sensorineural loss of hearing for high frequency sounds due to cisplatin. Renal function is normal. The treatment resulted in long-term survival for 12 years, and the patient is now able to work full time in a metal factory.

DISCUSSION

Etiology

There is now increasing evidence for an etiologic role of EBV [15,16] in carcinoma of the thymus with lymphoepithelioma-like histology. Histopathologically it has striking similarities with nasopharyngeal carcinoma, which has been associated with EBV for a long time [17,18]. Interestingly, both thymus and nasopharynx embryologically arise from the primitive foregut. There is one report in which no EBV could be detected in three carcinomas classified as lymphoepithelioma-like [19]. More recently, Matsuno examined 26 thymomas and demonstrated EBV DNA in only the one case that was histopathologically diagnosed as lymphoepithelioma-like carcinoma [10]. This is confirmed in our case: EBV could be demonstrated in the tissue of a tumor that was diagnosed as lymphoepithelioma-like carcinoma in 1981, when there were no specific techniques available. EBV was specifically detected by in situ hybridization of a DNA probe to EBV-encoded small ribonucleotides (EBER). EBER are transcribed during latent infection with the EBV virus, and high copy numbers are present in the nuclei of infected cells.

Clincial Features

Our case underlines the potential aggressiveness of malignant thymoma in children. Local invasion of the tumor into lungs, great vessels, pleura, and pericardium, as well as compression of trachea and esophagus, were observed. Our patient developed a distant metastasis to

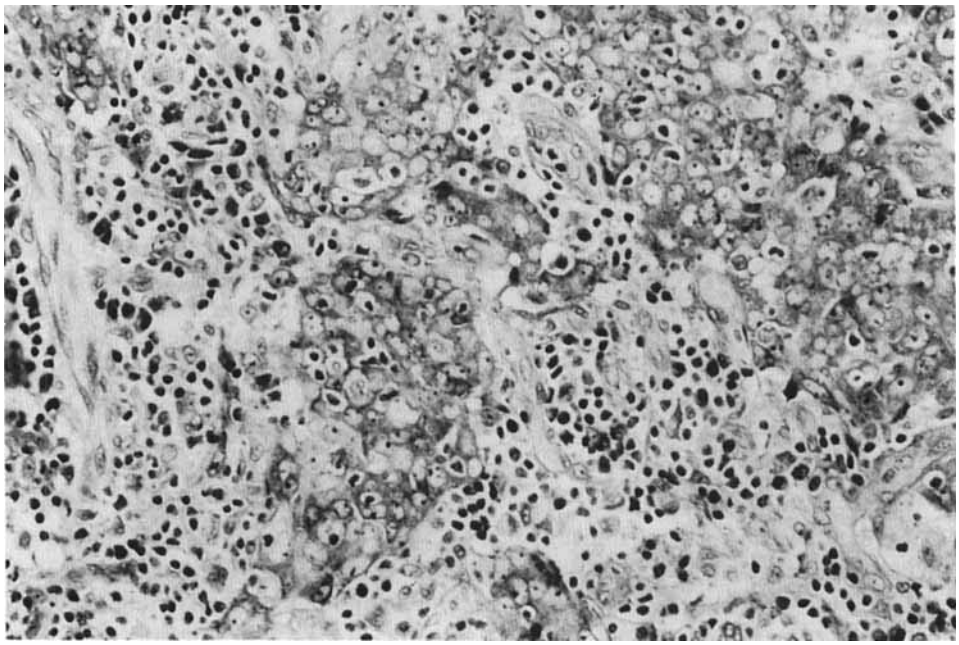

Fig. 1. Lymphoepithelioma-like carcinoma of the thymus. The medium-sized tumor cells are arranged in ill-defined sheets surrounded by lymphoid cells. The histologic and cytologic pattern of the tumor is indistinguishable from that in undifferentiated carcinoma of nasopharyngeal type (lymphoepithelioma or Schmincke-Regaud tumor). Giemsa stain, 280×.

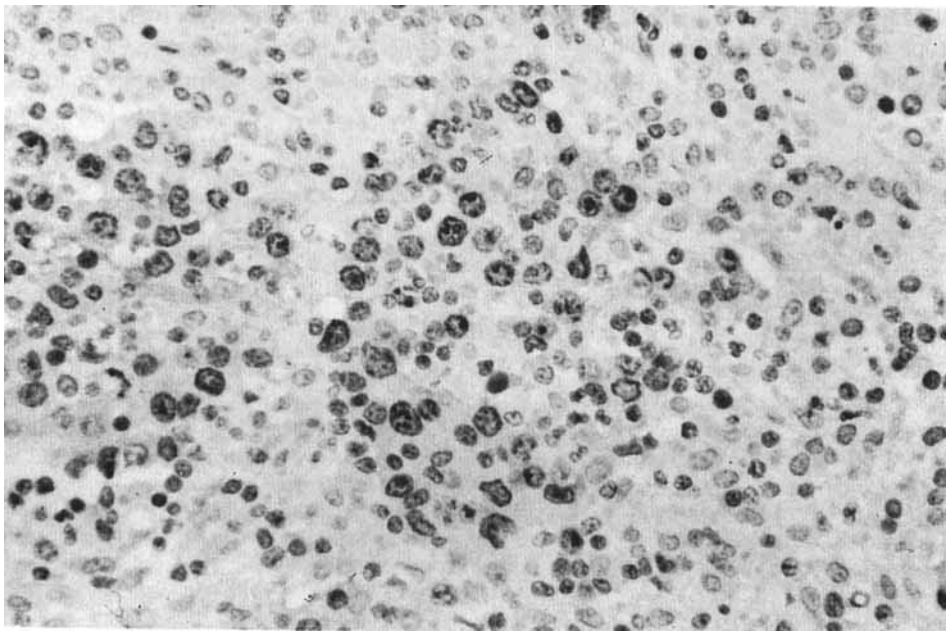

Fig. 2. Lymphoepithelioma-like carcinoma of the thymus. Strong nuclear expression of EBER (EBV-encoded small ribonucleotides; the black stained reaction product). In situ hybridization, immunohistochemistry using immune complexes of alkaline phosphatase, and monoclonal anti-alkaline phosphatase (APAAP-method) were used, 350×.

an extrathoracic site (cervical lymph node) despite intensive treatment. In pediatric cases described by others, spinal canal, liver [7,8], and distant skeletal metastases [7,8,11] have occurred. The most recent case of a lymphoepithelioma-like carcinoma [13] has striking similarities to our case (periosteal new bone formation, clubbing,

TABLE II. Staging System for Malignant Thymomas According to Masaoka [24]

I	Macroscopically completely encapsulated and microscopically no capsular invasion
II	(1) Macroscopic invasion into surrounding fatty tissue, mediastinal pleura, or both (2) Microscopic invasion into capsule
III	Macroscopic invasion into neighboring organ, such as the pericardium, great vessels, and lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

lymph node metastasis). It was reported before completion of therapy.

Histology and Outcome

Due to the rarity of thymomas in children, a histological subclassification has not been established, and a correlation between histological type and clinical course is not possible. Tumors were classified as thymic carcinomas in only 5 of the 40 pediatric cases reviewed [9,10,13]. In adults retrospective studies [20] and case reports [10,15,21] indicate a very poor outcome for thymic carcinomas with lymphoepithelioma-like histology. It therefore seems likely that the long-term remission reported here reflects the effect of aggressive therapy more than a subtype of thymic carcinoma with a somewhat favorable histology.

Surgery

Surgical evaluation will be the first step, as there are no non-invasive diagnostic investigations for malignant thymoma available. Complete resection of the tumor correlates with improved survival in the adult population as demonstrated in retrospective studies [22,23]. There are very few pediatric cases in which encapsulated non-invasive stage I [6] or stage II (for the staging system, see Table II) [24] thymic masses were found intraoperatively and complete surgical resection alone resulted in sufficient treatment [6,25]. It was, however, not stated clearly that these neoplasms were truly epithelial. Complete resection was not possible in our case and in the majority of cases described by others.

Combination Chemotherapy

Very limited information is available about the treatment of pediatric malignant thymoma with intensive combination chemotherapy. In malignant thymomas of category I, the use of adjuvant chemotherapy has resulted in the few long-term remissions described [4,6,11,12]. In adults cisplatin has been reported to be most active in thymoma and thymic carcinoma [26] (Table III). In contrast, the use of cisplatin has not been documented in any of the pediatric cases reviewed. In our patient long-term remission was induced by using a cisplatinum-containing regimen. Concerning dosage, we used two to five times the total dose of cisplatin and more than 20% higher total

TABLE III. Treatment and Outcome of Thymic Carcinoma in Children and Adults

	n	Age (yrs)	Histology, etiology	Therapeutic regimen	Outcome
Taylor [21], 1988	2	28, 43	Lymphoepithelioma-like, n.d.	Cisplatin, cyclophosphamide, doxorubicin, vincristine, methotrexate, and radiation therapy	Dead 28–36 mo after diagnosis
Weide [27], 1993	4	33–55	Undifferentiated (n = 3), Squamous cell (n = 1), n.d.	Cisplatin, etoposide, bleomycin, and radiation therapy	2 complete responses, 1 partial response, but survival <2 y
Dy [28], 1988	4	22–46	Undifferentiated, n.d.	Cisplatin, bleomycin, vinblastine, and radiation therapy	2 patients alive 4 and 6 y after completion of treatment
Dimery [16], 1988	1	30	Lymphoepithelioma-like, EBV associated	Cisplatin, cyclophosphamide, doxorubicin, prednisone + intensification with cyclophosphamide cisplatin, etoposide, and radiation therapy	Alive 24 mo after diagnosis
Levyraz [15], 1985	1	19	Lymphoepithelioma-like, EBV associated	Cisplatin, bleomycin, doxorubicin, prednisone, and radiation therapy	Dead 11 mo after diagnosis
Matsuno [10], 1992	1	10	Lymphoepithelioma-like, EBV associated	Intensive radiation and chemotherapy (details not given)	Dead 3–15 mo after diagnosis
Ramon y Cajal [9], 1991	3	10–14	Undifferentiated (n = 1), small cell (n = 2), n.d.	Resection, radiation and chemotherapy (details not given)	Dead 3–15 mo after diagnosis

n = number of patients; y = years, mo = months; n.d. = not determined.

doses of doxorubicin and ifosfamide compared with the adult dosages [16,29,30,31]. Interestingly, cisplatin-containing regimens also seem to have an effect on nasopharyngeal carcinoma [32,33].

As far as this single case allows, a conclusion on the usage of cisplatin, ifosfamide, and etoposide in even higher doses than in adults might be justified in light of the rapid disease progression in children. Caution is necessary with doxorubicin because of its potential to cause myocardiopathy. Toxicity was tolerable, although there was a loss of hearing for high frequency sounds due to a high cumulative dose of cisplatin (1,400 mg/m^2) as additional therapy for the relapse.

Radiation Therapy

The radiosensitivity of malignant thymomas and nasopharyngeal carcinoma has been documented in numerous pediatric and adult studies [6,32,34–37]. However, irradiation (40 Gy) of a pediatric thymic carcinoma combined with initial cyclophosphamide, epirubicin, and vincristine chemotherapy failed to reduce tumor size [13]. In our case the primary tumor, as well as the relapse in a cervical lymph node, responded to irradiation with 40 Gy. A synergistic effect of radiation with chemotherapy is to be expected and appears to be confirmed in our case. Thus radiation of at least 40 Gy to the tumor in combination with cisplatin-containing chemotherapy seems to be warranted.

From the limited data available and the experience of our case, we conclude that the child with malignant thymoma deserves most intensive treatment. Combined-modality treatment with a cisplatin and ifosfamide–containing multigent chemotherapy regimen, high dose irradiation to the tumor, and extensive, and if possible complete, resection of the tumor seems favorable.

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